Education, diet, and incident cardiovascular disease

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Education, diet, and incident cardiovascular disease: ecological interactions and conclusions

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See Articles page e748

The Prospective Urban Rural Epidemiologic (PURE) study[1] is an impressive epidemiological undertaking, coordinating clinical examinations and multi-year follow-up across more than 18 countries with more than 180 000 participants. This study is a successor of the Seven Countries study,[2,3] which was led by Ancel Keys and was done across seven countries with more than 12 000 participants. Keys made the fundamental observation that coronary heart disease and, correspondingly, serum total cholesterol differ dramatically across cultures, and he strongly asserted that diet is important in between-country differences.[3] The Seven Countries study used 7-day weighed diet in 16 cohorts of subsets of men, and it only examined diet ecologically. Keys said "it would be prohibitively expensive and wholly unfeasible" to attain enough repeated measures to estimate true individual participant means of habitual diets;[4] individual practical Food Frequencies Questionnaires (FFQs) were not yet available 60 years ago, when the Seven Countries study was initiated. The PURE study[1] used FFQs in participants of both sexes and included cohorts within countries that were diverse enough to study socioeconomic status. Keys[5] selected countries to maximise a priori between-country differences in diet and coronary heart disease, whereas PURE[1] selected countries to maximise and represent countries with a broad range of gross national product per capita values. Both studies[1,5] had the practical restriction of requiring willing and competent investigators in the target countries.

In their Article in *The Lancet Global Health*, Annika Rosengren and colleagues[6] used PURE data to study individual educational attainment relative to incident cardiovascular disease and total death. The main finding was that low individual educational attainment predicted higher incidence of both outcomes, and disproportionately so in low-income countries. This finding was despite a relatively low prevalence of hypertension and diabetes in these people, but this result was also accompanied by high 28-day case fatality rates. Rosengren and colleagues[6] concluded that poor access to health care is the dominant factor in these associations. However, the most common forms of cardiovascular disease are almost universally linked to risk factors. It is natural to wonder whether the cardiovascular disease in low-income countries among individuals with low education has atypical pathology. The disease incidence ascertainment method, relying heavily on participant and family reporting, would admit such a difference in pathology. However, the low education group in low-income countries is not actually free of cardiovascular disease risk factors: the diet score is directly correlated with individual educational attainment, and there were enough people who smoked (28%), had hypertension (29%), or diabetes (8%) for typical cardiovascular disease to be concentrated in these people. The authors do not present risk factor or behaviour relationships with cardiovascular disease incidence, so it is hard to judge the extent to which cardiovascular disease in this subset of PURE might be atypical. Our suggested conclusion is tempered, emphasising poor health behaviours along with poor access to primary and secondary health care. This is an important distinction for policy making.

A note on the statistical methods in the PURE work is revealing. Rosengren and colleagues[6] estimated individual-level associations with reasonably aggregated ecological units, namely low-income, middle-income, and high-income countries, then looked for individual-by-ecological interactions. This approach is what unveiled differential education-by-cardiovascular-disease associations by ecological grouping. The Seven Countries study[7] used a similar strategy in assessing whether serum cholesterol had the same association with mortality from coronary heart disease across six country groupings. The figure in the Seven Countries study[7] shows the mortality rate associated with coronary heart disease on the *y*-axis, serum cholesterol concentration on the *x*-axis, and six separate line graphs plotted, each indicating individual participant-based rate of coronary heart disease for a quartile of serum cholesterol within a subset of the seven countries. The ecological associations (between countries) are then seen as vertical differences. These graphs, scanned horizontally, revealed an increase in mortality from coronary heart disease with serum cholesterol in all country groupings except for Japan (a result that was

ambiguous because almost no one in the Japanese cohort had high cholesterol) yet, looking vertically in the display between countries, there were differential mortality rates associated with coronary heart disease between each country-pair (eg, northern Europe and the USA had higher rates than did southern Europe within each group of cholesterol concentrations). This important nuance suggests that serum cholesterol is causally important, but other factors must also be operating, and the association was possibly very weak in Japan. Only the individual-by-ecological interaction would reveal this pattern of association.

It is very tempting and common in analysis of data gathered over ecological units to pool the data without reference to the ecological unit. Mahshid Dehghan and colleagues[8] used this approach in studying total fat and total carbohydrate intake in the PURE study. Among their conclusions were that "high carbohydrate intake was associated with higher risk of total mortality" and that "global dietary guidelines should be reconsidered in light of these findings". These are inordinately strong statements. Additional care must be taken in several respects. First, ecological variables do not necessarily have the same meaning as the individual variables with the same name;[9] for an extreme example, in random population samples, female sex is present in 50% of people, but this finding reflects population structure, not related sex-specific biology such as sex hormones. Second, examination of total carbohydrate or total fat ignores the effects of individual fatty acids and carbohydrates and dietary quality in general. Application of the methods of Rosengren and colleagues[6] or Verschuren and colleagues,[7] and addition of a general diet pattern score (such as was used in the study by Rosengren and colleagues), has the potential to provide a clearer answer, addressing total carbohydrate in the context of how the rest of the diet might differ among countries. This approach might merit consideration in actions that depend on the truth of underlying causal assumptions, such as in formulating global dietary guidelines.

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